1356

USE OF HONEY IN MEDICINAL PREPARATIONS

by Drs. Alfonso R. Gennaro, Catherine N. Sideri, Nathan Rubin and Arthur Osol
School of Chemistry, Philadelphia College of Pharmacy and Science

A brief summary of the findings of research performed under a contract supervised by the Eastern Utilization Research and Development Division of the Agricultural Research Service is reported, as follows:

(1) Honey may be used as a vehicle to produce palatable preparations of excellent stability of riboflavin, a mixture of riboflavin and thiamine, ferrous sulfate, a mixture of sulfadiazine, sulfamerazine and sulfamethazine, and various formulations for treatment of cough. (2) Honey may also be used to produce palatable, but not very stable, preparations of ascorbic acid, thiamine, and aspirin. (3) Medicinal preparations containing honey may be preserved against microbiological deterioration with 0.05 per cent sorbic acid. (4) Specifications for pharmaceutical grade honey were developed.

Although honey has been used as an ingredient of medicinals since ancient times, very little information of the type required in present-day medicinal product formulation is known about it, a lack which has no doubt been responsible for the failure to use honey more widely in the pharmaceutical industry.

Before honey can be used as a vehicle in a medicinal product that may not be consumed for many months after its manufacture, it is essential to learn several things about the contemplated product: (1) Will the active ingredient or ingredients remain stable in the presence of honey? (2) is spoilage by microbiological organisms likely to occur and, if so, what may be done to prevent it? (3) will the use of honey impart a taste at least as good, if not better, than that of the same type of preparation without honey? (4) can the manufacturer *always* obtain honey of the required quality and so uniform that there will be no noticeable difference in his product from one batch to another? These are the questions that a 2-year investigation of the potential utility of honey in medicinal products, performed in the laboratories of the School of Chemistry of the Philadelphia College of Pharmacy and Science, under a contract with the U. S. Department of Agriculture,* has sought to answer, and the results of which study are summarized in the following.

CHEMICAL STABILITY STUDIES

Vitamins - Honey solutions of the common water-soluble vitamins were studied under various conditions of preparation and storage; the vitamins used were thiamine (vitamin B_1), riboflavin (vitamin B_2), cyanocobalamin (vitamin B_{12}), and ascorbic acid (vitamin C). Riboflavin, used in the form of sodium riboflavin-5'-phosphate, proved to be the most stable of these vitamins in honey solutions, if the solutions were stored in brown bottles. The stability of thiamine in honey was not as good as in other solutions containing no honey, though in combination with riboflavin it was more stable than when used alone. Honey solutions of ascorbic acid, and especially of cyanocobalamin, did not meet the long-term stability requirements for commercial preparations of this type. It should be noted, however, that honey would be an excellent vehicle for "extemporaneous" preparation of all these vitamins; that is, for compounding solutions that a physician many direct a pharmacist to make, on prescription order, for use during a limited time of two or three weeks.

Ferrous Sulfate - A popular iron tonic preparation of *The Pharmacopeia of the United States of America* is "Ferrous Sulfate Syrup," which is a solution of ferrous sulfate in sugar syrup, flavored with peppermint spirit. A similar preparation made with honey as the vehicle and sole flavor was entirely stable over the period of 11 months that it was studied, and it was exceptionally palatable and free of the astringent after-taste that is characteristic of most iron-containing preparations.

Sulfonamides - The "sulfa" drugs are among the most important of medicinals, and are commonly marketed in the form of liquid "suspensions." Because mixtures of sulfadiazine, sulfamerazine, and sulfamethazine are especially useful, preparations containing these "sulfa" drugs suspended in a vehicle composed mostly of honey were studied. These turned out to be not only completely stable, but they had the further very desirable characteristics of settling very slowly, of being readily resuspended by moderate shaking, and of being exceptionally palatable. A "taste panel" preferred the product made with honey over other, commercially-available, preparations.

Preparations for Cough - A number of preparations for cough were made with honey as the vehicle. Two of these, containing among other ingredients antihistaminic agents and either codeine or dihydrocodeinone, were not only exceptionally palatable, and effective, but remained free of sediment for the period of more than a year during which they were observed. A terpin hydrate elixir, long popular as a preparation for treating cough, was also prepared in palatable and stable form using honey as the vehicle.

Aspirin - Suspensions of aspirin in vehicles containing honey were prepared in seeking a stable liquid formulation of this important medicinal. While it was not possible to devise a preparation having long-term stability, a palatable product undergoing only 5 per cent hydrolysis in two days was prepared; such a preparation would be eminently satisfactory for "extemporaneous" preparation on prescription and would be ideal for administration to infants and young children.

Miscellaneous Preparations - A number of "elixirs" recognized as standard medicinals in either *The Pharmacopeia of the United States of America* or *The National Formulary* were modified to include honey. These "elixirs" were phenobarbital, pentobarbital, compound glycerophosphates, rhubarb and soda, iron and ammonium acetate, pepsin and rennin, compound pepsin, compound opium and glycyrrhiza, iron, quinine and strychnine, and terpin hydrate and

---

*A report of work done under contract with the U. S. Department of Agriculture and authorized by the Research and Marketing Act of 1946. The contract is being supervised by the Eastern Utilization Research and Development Division of the Agricultural Research Service.

codeine. In no instance, however, did the use of honey provide any notable advantage.

PRESERVATION AGAINST MICROBIOLOGICAL DETERIORATION

It was early apparent that medicinal products prepared with honey, containing also some water, were prone to decomposition by microbiological organisms. In order to determine how to prevent such deterioration, honey solutions were deliberately contaminated with organisms of *Bacillus subtilis*, *Proteus vulgaris*, and *Penicillium notatum*, respectively, and one or another of the antimicrobial agents sorbic acid, sodium benzoate, and mixtures of methylparaben and propylparaben was added. Complete preservation against deterioration was achieved by adding 0.05 per cent (weight-in-volume) of sorbic acid to the honey solutions.

TASTE CHARACTERISTICS

All preparations were evaluated for taste which is, of course, a highly subjective criterion. Nevertheless, in all cases where honey proved to be a desirable medicinal product ingredient the taste of the preparation was judged by the majority of persons thus testing the preparation to be superior to that of similar solutions made without honey.

QUALITY SPECIFICATIONS FOR HONEY

Various floral types of honey were used in this study, all described as having been heat-processed and filtered. Some of the samples, however, required filtration, others being so clear that this treatment was not needed, a matter of considerable advantage to manufacturers who may find filtration of honey to be a cumbersome procedure. In those instances where filtration was necessary Celite Standard Super-Cel was used as a filter-aid, in amounts of 0.5 to 0.75 per cent, and the filtration was performed under 10 to 14 pounds of pressure. The following specifications for honey suitable for use in medicinal products are recommended:

General Description - Honey is the nectar of floral exudations of plants gathered and stored in the comb by honey bees, Apis mellifera Linne (Fam. Apidae). It must be heat treated for thirty minutes [140°F. - 160°F. (maximum)] and free from foreign substances such as parts of insects, leaves, etc., but may contain pollen grains. When graded according to the United States Standards for Grades of Extracted Honey (18 F.R. 52.1391 - 52.1404), it must be classified as "U. S. Choice" or "U. S. Fancy."

Moisture Content - Not more than 18.6 per cent, by weight. This corresponds to a refractive index ($nD^{20°}$) of not less than 1.4900, and a specific gravity (20°/20°C.) of not less than 1.4129.

Optical Rotation - Honey is levorotatory at 20°C.

Residue on Ignition - Not more than 0.40 per cent.

Artificial Honey - Introduce 10 ml. of a mixture of equal volumes of honey and water into a test tube and add 5 ml. ether. Shake gently and allow to stand until the ether layer is clear. Transfer 2 ml. of this clear ether solution to a small test tube and add a large drop of freshly prepared resorcinol solution (1 Gm. resorcinol in 100 ml. of hydrochloric acid of sp. gr. 1.18 - 1.19). A cherry red color appearing within one minute indicates the presence of artificial honey. Yellow to salmon shades have no significance.

Acidity - A solution of 10 Gm. of honey in 50 ml. of water requires not more than 5.0 ml. of 0.1N sodium hydroxide for neutralization, using phenolphthalein as indicator.

Color - Shall not be darker than Light Amber, when determined by use of the U.S.D.A. permanent glass color standards.

Floral Type - At the discretion of the manufacturer. (The addition of therapeutic agents to honey might alter its taste, and it appears advisable to leave the choice of the floral type to the manufacturer. Regardless of the floral type selected, honey should meet all other specifications).

Packaging and Storage - Honey should be stored in well-closed containers, and the temperature should not exceed 90°F. for a prolonged period. Honey that has granulated may be liquefied in its container by heating at a temperature not over 160°F. for 30 minutes, with occasional stirring.

ACKNOWLEDGMENT

The authors express their appreciation to Dr. Jonathan W. White, Jr., of the Eastern Utilization Research and Development Division of the Agricultural Research Service for his many helpful suggestions and other aid during this investigation.